Increasing Incidence of *Clostridium Difficile*-Associated Diarrhea in African-American and Hispanic Patients: Association with the Use of Proton Pump Inhibitor Therapy

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Background: *Clostridium difficile*-associated diarrhea (CDAD) has been increasingly diagnosed in hospitalized patients. The number of prescriptions for proton pump inhibitors (PPIs) has also increased significantly over time. Few studies have reported an association between CDAD and PPI use; however, the results are inconclusive.

Objective: To determine the relationship between CDAD and PPI use in African-American and Hispanic patients.

Methods: We retrospectively reviewed medical records of 640 cases with CDAD over nine years, diagnosed by the presence of C. *difficile* toxin in the stools. Age-/ sex-matched 650 patients with diarrhea but absent C. *difficile* toxin in stools were used as controls.

Results: Of the 640 cases, 576 (90%) received antibiotics and 32 (5%) received chemotherapy during the preceding three months. Of the 650 controls, 540 (83%) received antibiotics and 39 (6%) received chemotherapy during the preceding three months. CDAD was associated with the use of antibiotics or chemotherapy (OR=2.3, 95% CI: 1.5–3.7). Of the 608 cases receiving antibiotics or chemotherapy, 274 (45%) also received PPI within the preceding three months. Of the 579 controls who received antibiotics or chemotherapy, 169 (29%) also received PPI within preceding three months. CDAD was associated with the use of PPI (OR=2.0, 95% CI: 1.6–2.6).

Conclusion: Our findings indicate that PPI may be an emerging and potentially modifiable risk factor for CDAD and point out the importance of vigilance in prescribing PPI, particularly to patients who are hospitalized, taking multiple antibiotics and suffering from multiple comorbidities.

Key words: infectious diseases ■ diarrhea ■ gastric ■ African Americans ■ Latinos

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INTRODUCTION

The natural history of *Clostridium difficile*-associated diarrhea (CDAD) is evolving. Recent years have witnessed a significant increase in incidence, severity and mortality of CDAD.[1-3] In the past several years, there have been outbreaks of CDAD in various western countries, including the United States, Canada and the United Kingdom.[4,5] The annual healthcare cost for CDAD is estimated to exceed $1 billion in the United States alone.[6] This increase in the incidence has been noticed not only in the nosocomially acquired infections but also the community-acquired cases of CDAD. The exact reason for this increase in the incidence of CDAD remains unclear. However, possible contributing factors include: increased use of fluoroquinolone antibiotics,[7] development of resistance to antibiotics,[8] emergence of more virulent strains,[9] wide use of proton pump inhibitor (PPI) therapy leading to prolonged acid suppression and bacterial overgrowth, and yet unidentified factors.[10] Although the data pertaining to CDAD are widely available in the literature, this problem is not well studied in African-American and Hispanic patients. The purpose of our study was to determine the relationship between CDAD and the use of PPI in African-American and Hispanic patients.

METHODS

We identified and reviewed medical records of all African-American and Hispanic patients who were admitted to the hospital over a nine-year period (January 1997 to December 2005) with the diagnosis of diarrhea. The study was approved by the Charles R. Drew Universi-

ty institutional review board (IRB #06-03-946-01). We identified 684 patients with CDAD as diagnosed by the presence of *C. difficile* toxin in the stools. We excluded 44 patients because of incomplete data, leaving 640 patients for the study. Six-hundred-fifty age-/sex-matched patients with diarrhea but absent *C. difficile* toxin in stools were used as a comparison group. Sources of information for this study included inpatient and outpatient charts and gastroenterology consultation reports. We abstracted the demographic data (age, gender and race/ethnicity), diagnosis, use of antibiotics, chemotherapy and/or PPI, and presence or absence of comorbidity.

Data were analyzed using the two-tailed Chi-squared test to assess the statistically significant differences between the CDAD group and the comparison group for the use of PPI. In order to test the association between the presence of CDAD and the use of PPI, we calculated the odds ratio (OR) and the 95% confidence interval (CI) to compare the odds of using PPI in the group with CDAD relative to the odds of the use of PPI in the group without CDAD. Significance was defined by $p<0.05$. Statistical analyses were performed using SPSS® (Statistical Package for Social Science version 12, 2002; SPSS Inc., Chicago, IL).

RESULTS

The study included 640 cases, 18–101 years of age who were admitted to the hospital over a nine-year period and diagnosed with CDAD. Fifty-five percent of the CDAD patients were African American, and 45% were Hispanic. Fifty-five percent of the patients were female, and 28% were ≤65 years old (Table 1).

Six-hundred-fifty age-/sex-matched controls who were admitted to the hospital with diarrhea but absent *C. difficile* toxin (non-CDAD) were used as a comparison group. The age range for the patients in the comparison group was 18–97 years. Fifty-four percent of the non-CDAD patients were African American, and 46% were Hispanic. Fifty-four percent of the patients were female, and 26% were ≤65 years old (Table 1). There was no significant difference between the groups in the demographic characteristics (race/ethnicity) ($p>0.05$).

In the cases, the common comorbidities were hypertension, diabetes mellitus and malignancy. In controls, the common comorbidities were hypertension, malignant diseases and diabetes mellitus. There were no significant differences between the groups in relation to the presence of comorbidity ($p>0.05$) (Table 2).

Of the 640 cases, 576 (90%) received antibiotics dur-

Table 1. Demographic characteristics of patients with CDAD (cases) and without CDAD (controls)

	Cases (N=640)					Controls (N=650)				
Variables	African Americans (N=352)		Hispanics (N=288)		Total	African Americans (N=349)		Hispanics (N=301)		Total
	Males (N=158)	Females (N=194)	Males (N=130)	Females (N=158)	640	Males (N=158)	Females (N=191)	Males (N=139)	Females (N=162)	650
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age Group (Years)										
19–65	36 (22.8)	58 (39.9)	35 (26.9)	52 (32.9)	181 (28.3)	33 (20.9)	48 (25.1)	41 (29.5)	49 (30.2)	171 (26.3)
66–75	64 (40.5)	75 (38.7)	56 (43.1)	60 (40.3)	255 (39.8)	69 (43.7)	78 (40.8)	58 (41.7)	64 (39.5)	269 (41.4)
76–101	58 (36.7)	61 (31.4)	39 (30.0)	46 (29.5)	204 (31.9)	56 (35.4)	65 (34.0)	40 (28.8)	49 (30.2)	210 (32.3)

No significant differences in race/ethnicity, age, and gender between the groups ($p>0.05$)

Table 2. Comorbidities and mortality among patients diagnosed with CDAD and the comparison group (non-CDAD)

Variables	CDAD Group (N=640)	Control Group (N=650)
	N (%)	N (%)
Comorbidities		
Hypertension	122 (19.1)	131 (20.2)
Diabetes mellitus	112 (17.5)	101 (15.5)
Malignancy	87 (13.6)	105 (16.2)
Renal failure	67 (10.5)	58 (8.9)
Respiratory failure	48 (7.5)	39 (6.0)
Colectomy/colitis	15 (2.3)	5 (0.8)
HIV/AIDS	45 (7.0)	36 (5.5)
Death*	90 (14.1)	46 (7.1)

Total numbers exceed 640 in the CDAD group and 650 in the control group because of the presence of >1 variable in the same patients; * Significant difference between the groups ($p<0.05$)

ing the preceding three months. Of 650 controls, 540 (83%) received antibiotics during the preceding three months. CDAD was significantly associated with the use of antibiotics (OR=1.8, 95% CI: 1.3–2.6) (Table 3). Thirty-two (5%) cases and 39 (6%) controls received chemotherapy within the preceding three months. There was no difference in the use of chemotherapy between the groups (OR=0.8, 95% CI: 0.5–1.4) (Table 3).

We further analyzed the data to investigate the association between CDAD and the use of antibiotics or chemotherapy. We found that CDAD was significantly associated with the use of antibiotics or chemotherapy in our study population (OR=2.3, 95% CI: 1.5–3.7).

Of the 576 cases receiving antibiotics, 260 (45%) also received PPI within the preceding three months. Of the 540 controls who received antibiotics, 159 (29%) also received PPI within the preceding three months.

Relative to the group who was not using antibiotics or PPI, the use of antibiotics alone (OR=1.4, 95% CI: 1.0–2.0) or in combination with PPI (OR=2.8, 95% CI: 1.9–4.1) was associated with CDAD. The OR associated with the use of antibiotics and PPI was almost twice that with the use of antibiotic alone. The use of PPI did not differ between the groups by demographic characteristics of the patients (Table 4).

We analyzed the data adjusting for the use of antibiotics or chemotherapy to determine the independent association between CDAD and the use of PPI. Among patients who received antibiotic or chemotherapy, CDAD was significantly associated with the use of PPI (OR=2.0, 95% CI: 1.6–2.6). Among the group who did not receive antibiotics or chemotherapy, there was no association between CDAD and the use of PPI (OR=1.8, 95% CI: 0.7–4.7).

Controlling for the demographic variables, comorbidity, and the use of antibiotic or chemotherapy, CDAD was significantly positively associated with the use of PPI (adjusted OR=1.7, 95% CI: 1.4–2.2).

Of cases, 90 (14.1%) died. Of the 90 deceased cases, 51 (57%) received PPI. Of the controls, 46 (7.1) died. Of the 46 deceased controls, 27 (59%) received PPI. Cases had significantly higher probability of dying relative to the controls (OR=2.2, 95% CI: 1.5–3.2).

Among the PPI users, CDAD was not associated with mortality (OR=1.4, 95% CI: 0.8–2.3). Among the non-PPI users, CDAD was significantly associated with mortality (OR=2.9, 95% CI: 1.6–5.3).

We analyzed the data to determine if there was an association between mortality and the use of PPI stratified on the patient's disease status (cases and controls). Among the cases, the use of PPI was not associated with mortality (OR=1.7, 95% CI: 1.0–2.7). For the control group, the use of PPI was strongly associated with mortality (OR=3.5, 95% CI: 1.8–6.7).

DISCUSSION

Our study showed that CDAD was significantly associated with PPI use among our patient population. Previous studies on CDAD and its association with PPI did not report their results by race/ethnicity. Therefore, investigating association of PPI and CDAD in African-American and Hispanic populations is a distinctive characteristic of our study.

Although our study has the strength of focusing on the target population, it has important limitations. First, the retrospective cross-sectional design limited our ability to collect clinical data in a standard fashion. Second, our study patients were from a community hospital, and data thus obtained may not be applicable to unselected patients from the population at large. Most of the known risk factors for CDAD were measured and adjusted in both cases and controls in our study; however, severity of illness may be different in some patients, and sicker patients may be more susceptible to CDAD or there may be yet unidentified risk factors.

Although there is a consensus in the literature about the association of antibiotic use and CDAD, there is no accord with regards to association of PPI use and CDAD. Dial and colleagues showed that there was a 2.9-fold-higher likelihood of current PPI use among patients with

Table 3. Odds ratio and 95% confidence intervals for the use of antibiotics, chemotherapy and proton pump inhibitor, and the mortality for patients diagnosed with CDAD relative to patients without CDAD (comparison group)

Variables	CDAD Group (N=640) N (%)	Non-CDAD Group (N=650) N (%)	Odds Ratio (95% Confidence Interval)
Antibiotic use*	576 (90.0)	540 (83.1)	1.83 (1.3–2.58)
More than one antibiotic use	345 (53.9)	324 (49.8)	1.18 (0.94–1.47)
Chemotherapy	32 (5.0)	39 (6.0)	0.82 (0.5–1.37)
Proton pump inhibitor*$	274 (45.1)	169 (29.0)	2.13 (1.67–2.71)
Mortality*	90 (14.1)	46 (7.1)	2.15 (1.46–3.18)

Total numbers exceed 640 in the CDAD group and 650 in the control group because of the presence of >1 variable in the same patients; * Significant difference between the groups ($p<0.05$); $%: The percent from the total number of patients who received antibiotic and chemotherapy (n=608 in CDAD group and n=579 in the non-CDAD group).

Table 4. The use of proton pump inhibitor (PPI) among CDAD (cases) and non-CDAD (control) patients by demographic characteristics

	Cases (N=274)					Controls (N=169)				
	African Americans		Hispanics		Total	African Americans		Hispanics		Total
	Male	Female	Male	Female		Male	Female	Male	Female	
Variables	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age Group (Years)										
19–65	13 (8.2)	21 (10.8)	15 (11.5)	20 (12.7)	69 (25.2)	10 (6.3)	12 (6.2)	10 (7.7)	11 (7.0)	43 (25.4)
66–75	25 (15.8)	33 (17.0)	24 (18.5)	27 (17.1)	109 (39.8)	19 (12.0)	20 (10.3)	14 (10.8)	17 (10.8)	70 (41.4)
76–101	28 (17.7)	29 (14.9)	18 (13.8)	21 (13.3)	96 (35.0)	14 (8.9)	19 (9.8)	10 (7.7)	13 (8.2)	56 (33.1)

Percent from the total in the group; No significant differences in race/ethnicity, age and gender between the groups (p>0.05)

CDAD than healthy controls.[10] On the other hand, Loo and coworkers found that PPI exposure was not significantly associated with the development of CDAD.[11] Our finding of the association of CDAD and PPI use is consistent with other studies.[10,12,13]

Our study showed that there was no significant difference between the cases and controls in the use of chemotherapy. This finding was different from what is been reported in the literature.[12,14,15] This might be due to lower prevalence of use of chemotherapy in our patient population or an immunologic susceptibility or unidentified factor in our patient population. This finding calls for prospective research to investigate the association between CDAD and the use of chemotherapy among minority populations.

In our study, the majority of cases (90%) received antibiotics. In addition, we found that the use of antibiotics was relatively higher in cases than controls. In addition, CDAD was positively associated with the use of antibiotics, which is consistent with the literature.[8,12,13,15-17]

While the use of chemotherapy alone in our study was not associated with CDAD, the use of antibiotics or chemotherapy was associated with CDAD, and this association was stronger than that with the use of antibiotic alone. This might be due to an interaction between the use of chemotherapy and the use of antibiotics.

In our study, the use of PPI in combination with antibiotics was significantly associated with CDAD. On the other hand, CDAD was not associated with the use of PPI among patients who did not receive antibiotics or chemotherapy. These findings indicated that the use of antibiotics or chemotherapy affects the association between CDAD and the use of PPI in our study population. When we adjusted for the effect of the use of antibiotics or chemotherapy and the other confounding variables in the model, we found that the use of PPI was significantly associated with CDAD (i.e., the CDAD group had higher probability of using PPI relative to the non-CDAD group).[10,12,13]

Of the cases, 14.1% died, and this rate was higher than that of the control group. The mortality rate reported in our study was less than that reported by Pepin and colleagues (16.7%)[9] and was higher than that reported by Andrews and coworkers, (6.5%) among severe cases.[18] In our study population, mortality was not associated with the use of PPI, which is consistent with the other reports related to the safety of the drug.[19,20]

In conclusion, our findings indicate that PPI may be an emerging and potentially modifiable risk factor for CDAD and underscore the importance of vigilance in prescribing PPI, particularly to patients who are hospitalized, taking multiple antibiotics and suffering from multiple comorbidities.

The literature still lacks the evidenced-based cause-and-effect relationship between PPI use and CDAD. In addition, whether the benefits of PPI use in preventing acid-related disorders, such as stress-related mucosal damage, peptic ulcers and gastrointestinal bleeding, surpass their risk of causing CDAD and its complications remains unanswered yet.

In future, prospective controlled studies in minority patients are needed to elaborate upon the factors responsible for an increase in CDAD and the role of PPI use in this condition. Ultimately, the goal is to recognize and control the modifiable factors for increasing incidence of CDAD and decrease the associated morbidity and mortality.

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